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THERMAL PROPERTIES AND EUTECTIC BEHAVIOUR OF DAPIVIRINE IN COMBINATION WITH STEROID HORMONES AND OTHER ANTIRETROVIRALS

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It is well established that the melting point of a drug is inversely proportional to its lipophilicity [e.g. Calpena et al., J Pharm Sci, 83 (1994) 29-33] which, in turn, correlates with its ability to be absorbed in vivo. Therefore, if the melting point of a drug can be reduced without affecting other physicochemical parameters, then drug release and/or absorption may be enhanced. This general principle has been exploited in a number of marketed pharmaceutical products, including the topical anaesthetic cream EMLA[™] and the contraceptive vaginal ring Nuvaring[®]. Both products contain two active pharmaceutical ingredients - EMLA[™] contains a mixture of prilocaine and lidocaine, while Nuvaring[®] contains etonogestrel and ethinyl estradiol (Fig. 1). Each drug in these combinations serves to reduce the melting point of the other drug, much in the same way that salt reduces the melting point of water (explaining its use on icy roads). For example, the phase diagram for etonogestrel and ethinyl estradiol shows that the maximum reduction in drug melting point occurs for a 1:1 mixture (Fig. 2).



Figure 1. Examples of combination drug products formulated as eutectic mixtures.

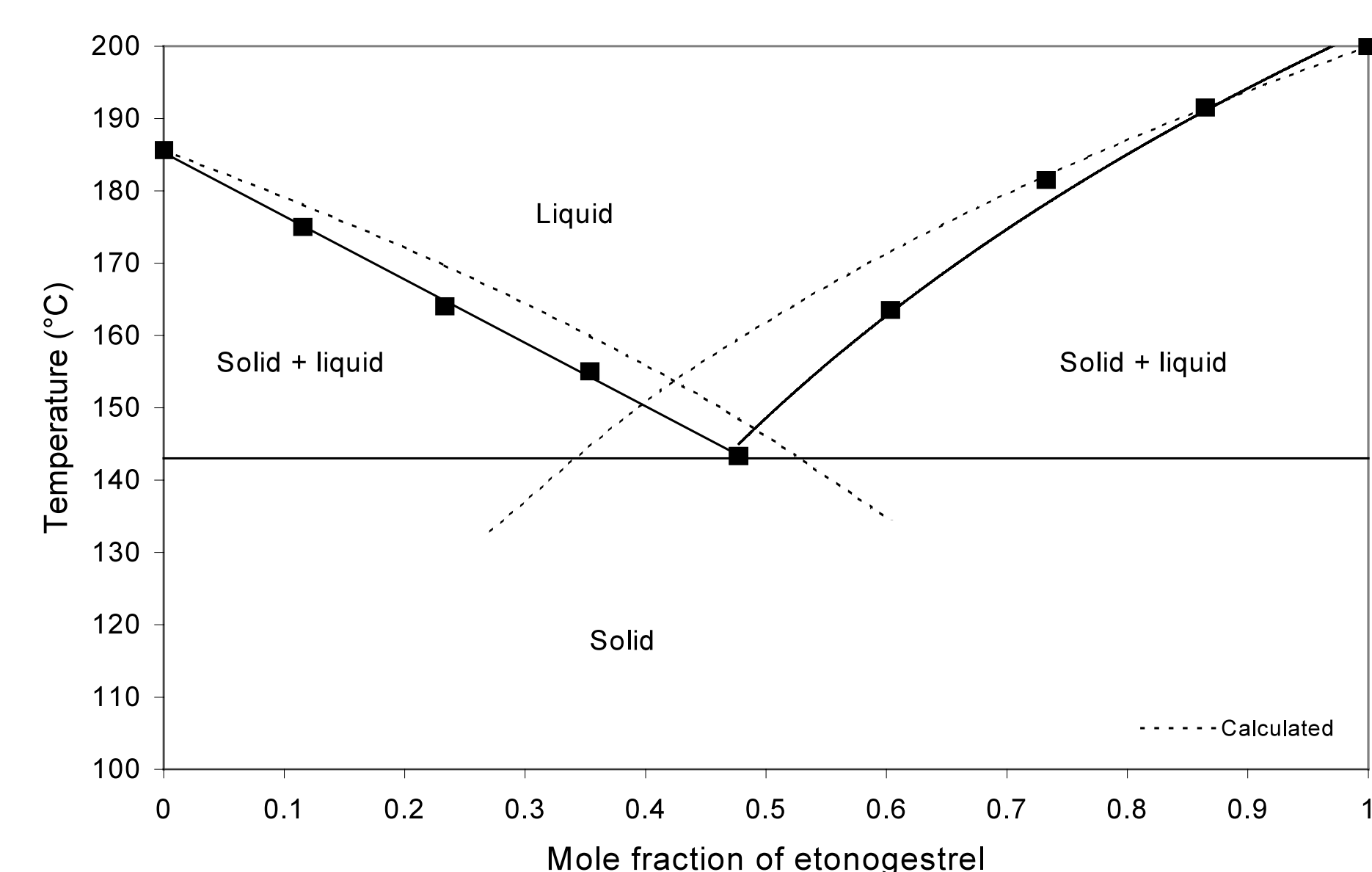


Figure 2. Phase diagram for etonogestrel and ethinyl estradiol, the drug components of Nuvaring [Van Laarhoven et al., Int J Pharm, 232 (2002) 163-173].

Combination microbicide and multi-purpose prevention technology (MPT) products in which the active pharmaceutical ingredients are intimately associated may also offer increased drug release / absorption on account of reduced

melting behaviour. Here, we report that the lead antiretroviral microbicide candidate dapivirine (DPV) consistently forms eutectic or reduced melting temperature compositions with various antiretrovirals and steroid hormones that might be included as part of a MPT product.

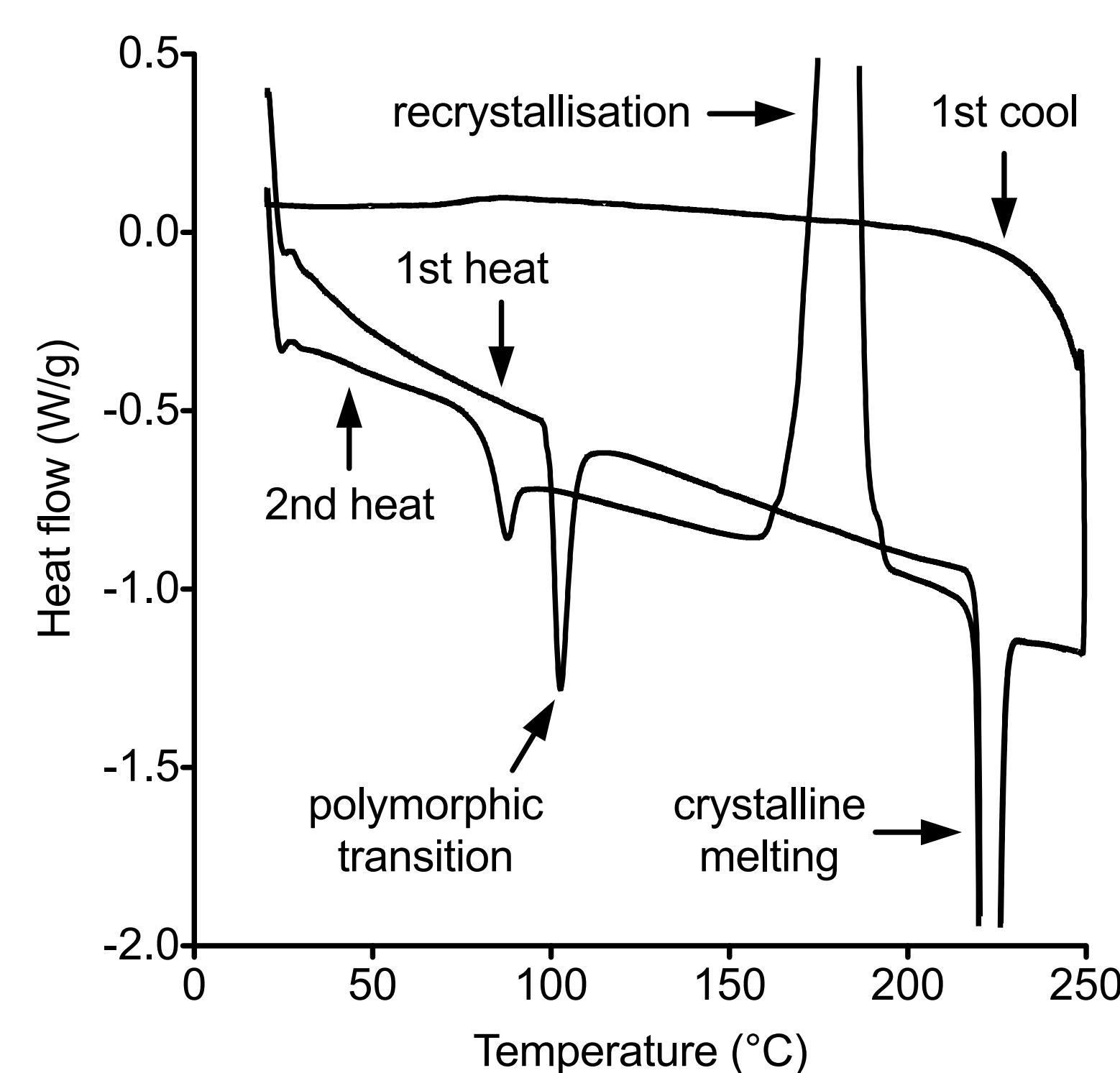


Figure 3. DSC thermogram showing thermal behaviour of DPV alone. During the first heating cycle, DPV shows a polymorphic transition at 105°C and a crystalline melt at 222°C. Following cooling, a second heat cycle shows a glass transition at 80°C, a recrystallisation process at 160°C and a subsequent crystalline melt at 220°C.

Figure 4. DSC traces showing thermal behaviour of DPV and LNG mixtures. DPV shows a polymorphic transition at 105°C and a melting endotherm at 220°C. All other combinations showed similar thermal behaviour.

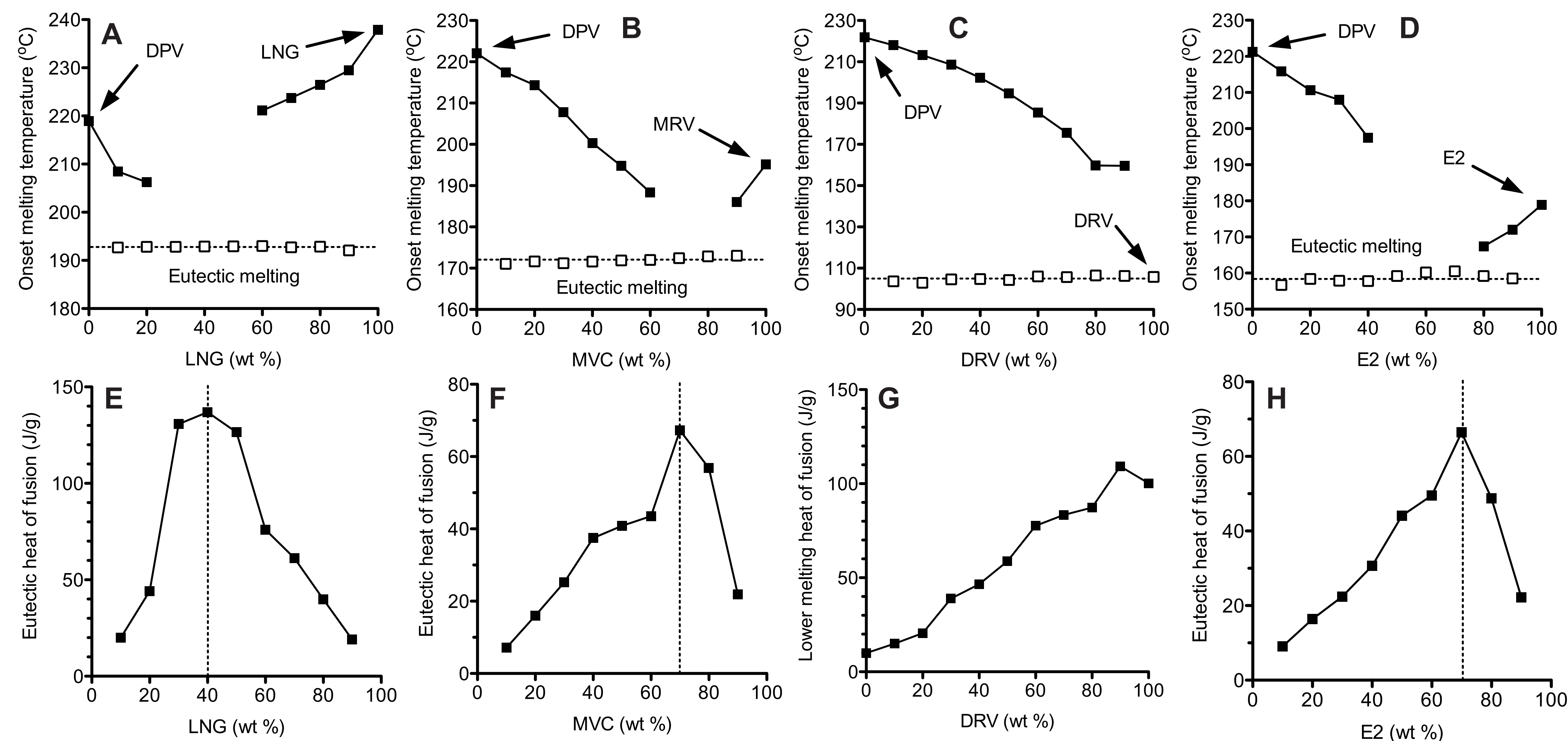
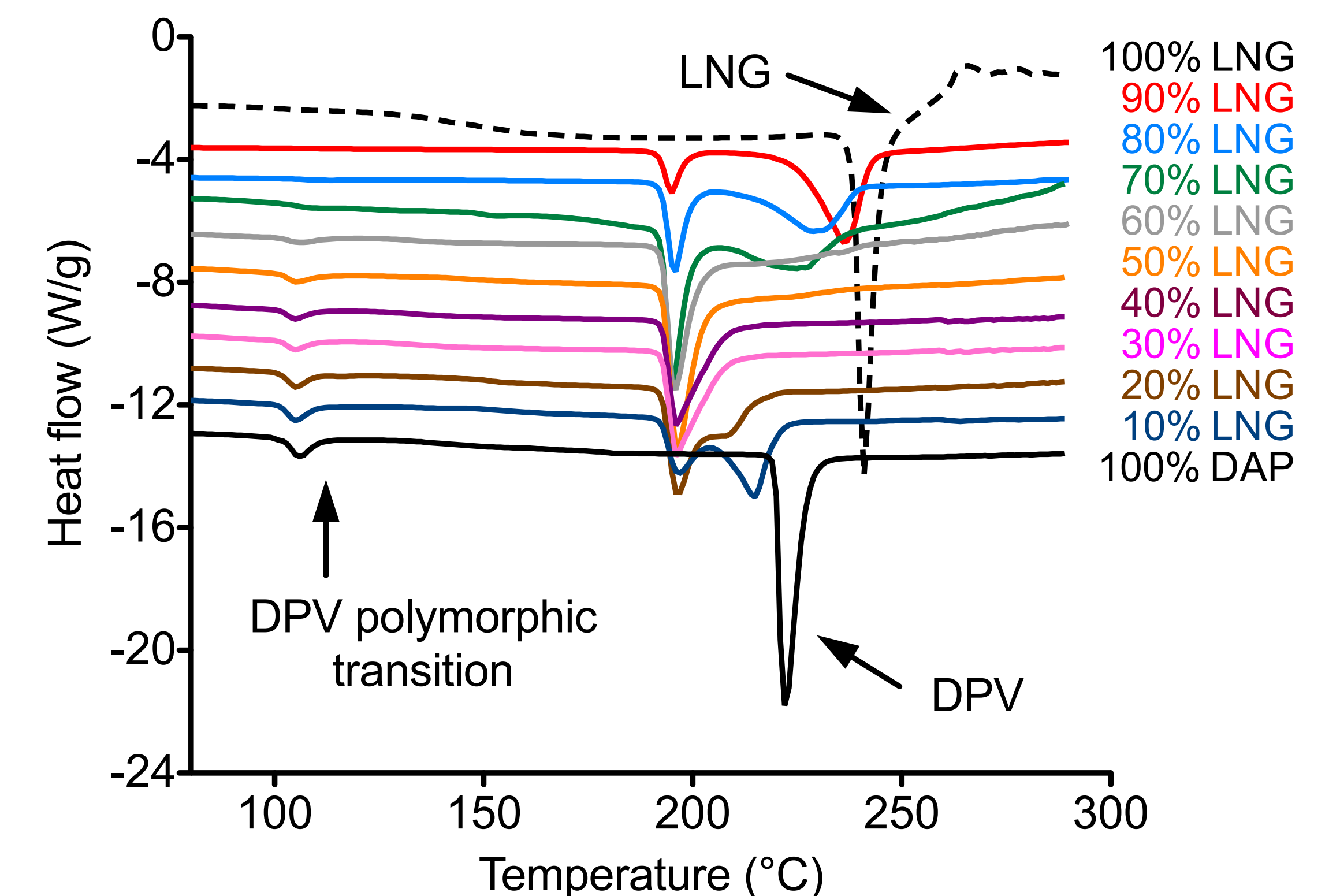


Figure 5. Phase diagrams for various dapivirine combinations. A - levonorgestrel (LNG), B - maraviroc (MVC), C - darunavir (DRV), D - 17 beta-estradiol (E2). According to figures E-H, the eutectic or lowest melting composition is determined as the composition having the largest heat of fusion value for the eutectic melting transition. These eutectic compositions are indicated by a dashed line.